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评 述
第二十八届中国科协年会学术论文　肿瘤免疫机制与生物药治疗专题

肿瘤相关成纤维细胞驱动胰腺癌上皮间质转化与化疗耐药

张少博, 曾琼, 刘明洋*

国家癌症中心, 国家肿瘤临床医学研究中心, 中国医学科学院北京协和医学院肿瘤医院, 分子肿瘤学全国重点实验室, 北京 100021
* 联系人: E-mail: liumy@cicams.ac.cn

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摘要　胰腺导管腺癌(pancreatic ductal adenocarcinoma, PDAC)具有高度侵袭性、易发生早期转移、对多种治疗手段反应不佳等临床特点, 其高度纤维化的肿瘤微环境被认为是推动疾病进展和治疗失败的重要基础. 微环境中的肿瘤相关成纤维细胞(cancer-associated fibroblasts, CAFs)作为关键成分, 其并非单一促瘤细胞群, 而是由iCAF, myCAF, apCAF及SenCAF, ifCAF, mapCAF等状态共同构成的动态生态系统, CAF可通过TGF-β/SMAD与非经典PI3K/AKT、MAPK信号、IL-6/STAT3炎症轴、CXCLs-CXCR2趋化网络、ECM-整合素-FAK/YAP力学传导以及细胞外囊泡/非编码RNA货物传递等多条主线, 诱导PDAC细胞发生上皮间质转化(epithelial-mesenchymal transition, EMT)、肿瘤干细胞样特性增强、局部浸润和远处转移. 与此同时, CAF通过基质高压和药物渗透障碍、细胞黏附介导耐药、代谢供给、免疫排斥及治疗诱导状态转换等机制共同塑造化疗耐药. 近年来, 单细胞测序、空间转录组学、多组学整合及功能筛选研究持续拓展了对CAF来源、异质性、空间生态位与可塑性的认识, 并推动CAF研究由"单一的促瘤细胞群"的粗略框架, 转向"不同亚群、特异功能及细胞间时空互作"的机制解析. 本文系统地梳理了CAF促进胰腺癌EMT与化疗耐药的分子机制, 并整合了近年关于CAF异质性及精准干预策略的研究进展, 旨在从机制层面概括CAF驱动PDAC恶性进展的关键路径, 并讨论靶向CAF亚群与联合治疗在未来转化研究中的潜在价值.

关键词　胰腺导管腺癌, 肿瘤相关成纤维细胞, 上皮间质转化, 化疗耐药, CAF异质性

胰腺癌是当今世界上恶性程度最高的实体肿瘤之一, 具有极强的局部侵袭能力, 且往往在早期即出现转移, 病死率极高[1]. 大多数患者在确诊时已处于局部晚期或转移阶段, 由于其对传统放疗和化疗普遍不敏感, 并且对靶向治疗及免疫治疗的反应不佳, 胰腺癌的整体预后迄今仍不理想. 手术切除仍是目前唯一可能实现根治的治疗方式, 但80%的患者术后仍会因局部或远处转移而复发, 进而导致治疗失败[2]. 根据美国癌症协会2026年癌症统计数据, 胰腺癌在美国预计新增病例数为67530例、死亡52740例; 尽管综合治疗不断进展, 其总体5年相对生存率仍约为13%[3]. 胰腺癌中常见的基因突变包括*KRAS*, *TP53*, *CDKN2A*和*SMAD4*. 95%的胰腺癌患者中存在*KRAS*突变, 在LSL-*KRAS*G12D(KC模型)[4]中, *KRAS*突变导致了胰腺上皮

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内瘤变(PanIN)的形成, 而在*KRAS*G12D, *TP53*突变及Cre模型(KPC模型)[5]中, *KRAS*突变伴随随后的*TP53*突变诱导了胰腺癌的发生. 然而, 针对上述基因变异(尤其是*KRAS*)的靶向治疗却未能延长胰腺癌患者的生存期[6]. 因此, 当前亟需提出新的干预策略以阻止胰腺癌进展和转移. 胰腺癌微环境高度复杂, 以致密的间质分布为显著特征, 其微环境中约80%~90%为基质成分. 该基质并非功能惰性的被动支架, 而是可主动塑造PDAC细胞的生物学行为, 并促进化疗耐药形成. 已有研究表明, 间质成分丰富的胰腺癌患者对临床治疗的反应更差[7,8]. 然而, 胰腺癌基质如何促进肿瘤进展及化疗耐药的分子机制仍不明确.

1 胰腺癌相关成纤维细胞

胰腺癌微环境以显著的促结缔组织增生反应和高度纤维化间质为重要特征, 主要由肿瘤相关成纤维细胞(cancer-associated fibroblasts, CAFs)、细胞外基质(extracellular matrix, ECM)、免疫细胞、内皮细胞、周细胞及神经成分等共同构成[7]. 其中, CAF是胰腺癌微环境中最活跃的组成部分之一.

1.1 CAF来源与经典亚型

CAF起源于胰腺星状细胞、骨髓间充质干细胞(mesenchymal stem cells, MSCs), 也可由脂肪细胞、周细胞、平滑肌细胞和内皮细胞转分化而来. 其复杂的细胞来源决定了CAF的显著异质性. 根据表型与功能差异, CAF可分为不同的经典亚型, 包括炎症型CAF (inflammatory CAF, iCAF; IL-6, IL-1, LIF和CXCL12等分泌水平较高, α-SMA相对较低)、肌成纤维型CAF (myofibroblastic CAF, myCAF; α-SMA, TAGLN, POSTN及胶原相关基因表达较高, 常邻近肿瘤细胞并参与ECM沉积与力学重塑)以及抗原呈递型CAF(antigen-presenting CAF, apCAF; 表达MHC-II相关分子和CD74, 但通常缺乏经典共刺激分子). 需要强调的是, CAF亚型并不能简单等同于“促瘤”或“抑瘤”二分法, 其功能取决于空间位置、病程阶段、治疗暴露和与肿瘤/免疫细胞的互作背景. 这种来源和状态差异进一步奠定了CAF功能异质性的基础. 除细胞来源外, TGF-β, HGF, EGF, FGF和SHH等信号通路同样参与间质生成和CAF状态塑造[9~11]. CAF进一步分泌多种趋化因子、细胞因子、细胞外囊泡(extracellular vesicles, EVs)和ECM, 通过成纤维细胞活化、ECM重塑和免疫抑制来促进肿瘤进展, 并降低药物递送效率, 从而介导对化疗或免疫治疗的耐受[12].

1.2 CAF异质性、可塑性及空间特征

CAF异质性并非单纯的标志物差异, 而是贯穿PDAC发生发展全过程的动态生态特征, 可从时间演化、状态分化、空间定位及临床分层四个层面加以理解. 从肿瘤演进的早期阶段看, 多组学研究已显著拓展了对PDAC间质演化及CAF生物学的认识. 研究显示, 在胰腺癌的早期病灶周围已出现明显的免疫重塑与基质应答信号, 提示CAF相关微环境改变可能早于典型浸润性肿瘤形成[13]. 在癌前病变阶段即已存在上皮间质协同演化[14]. 随着病变进展至浸润性PDAC阶段, 不同肿瘤分子亚型与不同基质表型之间存在强烈的互作: 基底样型肿瘤(basal-like)更常伴随活化基质, myCAF/csCAF富集及免疫抑制程序, 而经典型肿瘤(classical)则与PanIN相关Hedgehog信号和PSC特征更为相关[15]. 并且, 肿瘤上皮MAPK活性可通过持续分泌TGF-β1驱动成纤维细胞向肌成纤维型CAF状态分化, 同时具有TGF-β、缺氧和免疫调节特征的亚群被定义为mapCAF亚群, 该表型与基底样型肿瘤及$CD8^+$ T细胞减少相关[16].

在此基础上, 更多具有功能指向性的CAF不断被识别. 衰老相关的肌成纤维细胞亚群可主导免疫抑制程序[17]. 具有干扰素应答特征并可能发挥肿瘤限制作用的ifCAF亚群也被鉴定出来[18]. $PLXDC1^+$肿瘤相关胰腺星状细胞更倾向于塑造促纤维化、免疫抑制性的基质生态[19]. 除状态谱系不断扩展外, 从空间和时间维度上看, CAF状态具有明显可塑性. 基于人源PDAC单细胞图谱, $CXCL10^+$成纤维细胞与basal-like肿瘤细胞在空间上显著共定位, 提示特定炎症/干扰素相关CAF程序与侵袭性上皮状态之间存在稳定的生态位耦联[20]. 对人胰腺癌样本的单细胞分析进一步表明, 成纤维细胞群体并非静态亚群, 而是沿炎症反应、基质沉积和免疫调节等轨迹连续转换, 其演化同时受疾病阶段与治疗暴露的塑造[21]. 这种可塑性并不完全依赖肿瘤细胞的外源性诱导, CAF内部状态网络本身亦可主动塑造免疫抑制性基质生态. 例如, CAF中*STK11*缺失可增强CAF之间的信号串扰、重塑细胞外基质程

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序, 并抑制MHC I相关抗原呈递, 从而推动免疫抑制性肿瘤微环境的形成[22], 提示CAF内在抑癌基因的失活也可能是驱动基质恶化的重要机制. 空间组学进一步将CAF异质性与局部扩散及转移联系起来. 通过对神经侵犯相关区域进行单细胞和空间转录组分析, 围神经生态位中富集到特定的施万细胞、myCAF及炎症髓系细胞程序, 提示CAF可与神经成分协同促进局部侵袭[23]. 在转移性PDAC中, 原发灶与转移灶之间存在持续的状态重编程, 而CAF及其所塑造的基质生态位构成转移适应的重要基础[24]. 由此可见, CAF异质性最终并不仅仅表现为局部生态位差异, 而是进一步投射为可识别的患者分层和治疗反应差异. PDAC可划分为iCAF-rich, myCAF-rich和PSC-rich三类CAF相关微环境亚型, 其中关键少数CAF亚群与巨噬细胞和肿瘤细胞存在高度互作[25]. 相应地, 基于CAF膜蛋白的多模态特征可用于预后评估和治疗反应预测, 这表明CAF分型正在从描述性分类迈向具有临床转化潜力的生物标志物框架[26]. 此外, 一类BNIP3高表达的成纤维细胞亚群兼具缺氧与炎症相关特征, 与不良预后及较差的免疫治疗反应相关, 再次提示缺氧相关CAF状态在侵袭性PDAC中具有重要分层价值[27]. 跨癌种整合单细胞与空间转录组分析进一步揭示, 肿瘤微环境中基质细胞具有跨瘤种保守的共性特征及潜在治疗靶点, 为基于CAF分层的精准干预提供了更广的视角[28]. 总体而言, CAF异质性并不只是标志物层面的差异, 而是对应着不同的空间位置、功能状态及与肿瘤上皮的互作方式. 正是这种状态分化和可塑性, 使CAF能够在EMT促进、耐药塑造及治疗反应调控中承担不同角色, 也构成了后文机制分析与干预策略讨论的基础, 关于胰腺癌中主要CAF亚群的标志物、功能及与EMT/耐药的关系见表1.

2 CAF促进EMT与肿瘤转移

上皮间质转化(epithelial-mesenchymal transition, EMT)是肿瘤细胞由上皮表型向间质表型动态转变的过程, 会伴随迁移侵袭能力的增强. CAF通过旁分泌信号刺激邻近的肿瘤细胞, 从而增强EMT进程并促进肿瘤转移, 其关键环节包括CAF诱导EMT相关转录因子表达及重塑肿瘤细胞状态. CAF能够分泌TGF-β, IL-1α/β, IL-6, CXCL12, FGF, EGF及TNF-α等多种细胞因子和趋化因子, 从而促进PDAC细胞存活、增殖及EMT发生[29]. 从机制上看, CAF促进EMT与肿瘤转移的过程主要涉及TGF-β信号、ECM重塑与力学转导、炎症因子及趋化因子网络、非编码RNA/胞外囊泡传递, 以及其他促转移因子与谱系重编程等几个层面, 见图1.

2.1 TGF-β

TGF-β是一种多能性细胞因子, 在CAF中呈高表

表 1 胰腺癌中主要CAF亚群的标志物、功能及与EMT/耐药的关系[a)]

Table 1 Markers, functions, and relationship with EMT/drug resistance of major CAF subpopulations in PC[a)]

亚群	主要标志物	主要功能特征	与EMT/耐药关系
iCAF	IL6, CXCL12, LIF, PDGFRA; α-SMA低/阴性	分泌IL-6, IL-1, LIF等促炎因子; 多由IL-1/JAK/STAT信号诱导; 多位于肿瘤细胞相对远端	通过IL-6/STAT3等轴促进EMT、化疗耐受和免疫抑制[8,11]
myCAF	α-SMA, TAGLN, POSTN, COL1A1, LRRC15	邻近肿瘤细胞; TGF-β响应强; 参与ECM沉积、胶原重排和组织硬化	经ECM-整合素-FAK/YAP机械传导促进EMT; 致密基质可降低药物渗透[8,11]
apCAF	MHC-II相关分子、CD74	具抗原呈递样转录特征, 但通常缺乏经典共刺激分子; 可与$CD4^+$ T细胞互作	可能通过诱导免疫抑制性T细胞反应间接影响治疗反应[8,11]
ifCAF	ISG15, IFIT1/3, MX1等干扰素刺激基因	干扰素应答特征明显; STING激动可诱导该状态	与肿瘤限制性和免疫激活相关, 提示可作为CAF重编程方向[18]
SenCAF	CDKN2A, p16, SASP因子(IL-6, CXCL1等)	衰老相关肌成纤维细胞; 具SASP并可累积于肿瘤导管周围	促进免疫抑制和治疗抵抗; 清除SenCAF可改善模型中的化疗响应[17]
mapCAF	MAPK高活性、TGF-β信号、缺氧和免疫调节基因	由肿瘤上皮MAPK活性维持TGF-β1分泌并驱动; 常富集于basal-like生态位	与$CD8^+$ T细胞减少、免疫排斥和治疗低反应相关[16]
$PLXDC1^+$ PSC	PLXDC1	位于侵袭性$LRRC15^+$ myCAF和$SPP1^+$巨噬细胞附近	塑造促纤维化、免疫抑制性肿瘤边界生态位[19]

a) ifCAF: interferon-response cancer-associated fibroblast; SenCAF: senescent cancer-associated fibroblast; mapCAF: MAPK-high cancer-associated fibroblast

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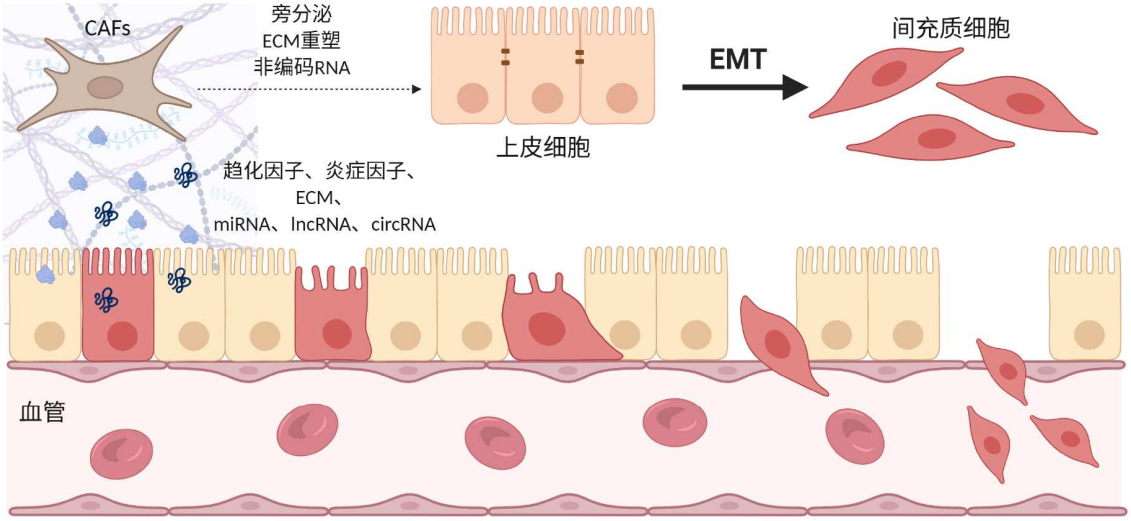


图 1 CAF通过旁分泌信号、ECM力学重塑与非编码RNA诱导肿瘤细胞EMT与转移. CAF可分泌TGF-β并经经典SMAD及非经典PI3K/AKT、MAPK通路诱导上皮间质转化; 通过重塑细胞外基质的成分、排列与硬度, 经整合素-FAK/YAP力学传导促进侵袭; 分泌IL-6等白细胞介素及CXCL趋化因子激活STAT3等炎症信号; 并通过细胞外囊泡携带miRNA, lncRNA, circRNA等非编码RNA货物对肿瘤细胞进行远程调控. 上述信号共同上调SNAIL, ZEB, TWIST等EMT转录因子, 并与肿瘤干细胞样特性相互耦联, 最终促进肿瘤细胞的迁移、侵袭与转移. 图件版权说明: Created in BioRender.com. Hu, Y. (2026) https://BioRender.com/prwowi0

Figure 1 CAFs induce epithelial-mesenchymal transition and metastasis of tumor cells via paracrine signaling, ECM mechanical remodeling and non-coding RNAs. CAFs secrete TGF-β to induce EMT through canonical SMAD and non-canonical PI3K/AKT and MAPK pathways; remodel the composition, alignment and stiffness of the ECM to promote invasion via integrin-FAK/YAP mechanotransduction; secrete interleukins such as IL-6 and CXCL chemokines to activate inflammatory signaling including STAT3; and remotely regulate tumor cells by delivering non-coding RNA cargo (miRNA, lncRNA and circRNA) through extracellular vesicles. These signals jointly upregulate EMT transcription factors (SNAIL, ZEB and TWIST) and couple with cancer stem cell-like properties, ultimately promoting tumor cell migration, invasion and metastasis. Created in BioRender.com. Hu, Y. (2026) https://BioRender.com/prwowi0

达, 可通过经典SMAD通路介导的转录重编程以及非经典通路介导的信号扩增与协同网络激活多种下游效应分子[30]. 经典SMAD通路: 经典SMAD通路是TGF-β诱导EMT的基础机制. CAF分泌的TGF-β与受体结合后, 可诱导Smad2/3磷酸化, 并与SMAD4形成复合物转位入核, 进而在转录水平上诱导Vimentin, Fibronectin, SNAI1, ZEB1和ZEB2等EMT相关标志物表达水平的上调, 从而促进EMT进程, 并伴随细胞黏附能力减弱及迁移侵袭能力增强[31]. 在结直肠癌中, CAF来源的TGF-β可通过SMAD4信号上调Snail并下调E-cadherin, 从而促进EMT[32]. 类似地, 在乳腺癌中, TGF-β1可通过阻断Smad2/3/4蛋白的降解来增强其稳定性, 进一步降低E-cadherin的表达并上调Vimentin, 从而促进EMT及肿瘤转移[33]. 除直接诱导EMT以外, TGF-β-SMAD4信号通路还可通过抑制FOSL1表达促进胰腺癌转移灶定植[34]. 这提示经典通路的作用并不限于表型转换本身, 还参与转移后期的生态位适应与扩增. 相应地, 动物体内实验结果显示, 采用TGF-β受体抑制剂LY2109761或KPF 3-O-G治疗可减少肿瘤的发生和转移[32,35]. 这些结果进一步说明, 经典SMAD通路是CAF-TGF-β轴的重要干预节点. 非经典通路及协同网络: 除经典SMAD依赖性转录调控外, CAF来源TGF-β还可通过激活多条非经典信号通路及其协同网络放大EMT效应[36,37]. TGF-β可激活PI3K/AKT和MAPK等非经典信号级联, 从而增强肿瘤细胞的生存、迁移和干性维持能力. 在肝细胞癌中, CAF来源的TGF-β1可上调TROY并激活PI3K/AKT/TBX3信号, 继而上调SOX2, NANOG和OCT4等干性相关因子的表达, 最终促进肝癌的EMT和化疗耐药; 靶向该轴则可削弱EMT并改善治疗反应[38]. 此外, TGF-β可通过依赖TRAF6泛素化的方式激活PI3K, 该过程并不依赖TGF-β Ⅰ型受体的激酶活性, 而是通过促进TGF-β Ⅰ型受体与PI3K调节亚基p85α形成复合物, 从而促进前列腺癌转移[39]. 这说明TGF-β非经典信号并非经典通路的附属分支,

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而是能够独立放大侵袭性表型的重要机制. TGF-β可通过影响EMT关键转录因子的蛋白稳定性, 延长EMT状态的持续时间. 例如, TGF-β可激活去泛素化酶USP27X, 后者能直接对Snail1进行去泛素化修饰并增强其稳定性, 最终介导Snail1依赖性的细胞侵袭和转移形成[40]. 由此可见, 非经典通路的作用并不只是"再激活一条信号", 而是可通过转录后调控和蛋白稳态层面进行调节, 使EMT由短暂诱导转变为更稳定的恶性状态. TGF-β还可与表观遗传程序及受体酪氨酸激酶网络形成协同放大, 进一步增强CAF驱动的转移能力. 在乳腺癌中, CAF来源的TGF-β通过激活SMAD2/3/4上调长链非编码RNA——HOTAIR的表达[41], HOTAIR作为重要的表观遗传调控分子, 进一步参与EMT相关转录程序的重塑, 促进肿瘤细胞迁移、侵袭及转移能力的增强. 肿瘤细胞来源TGF-β可诱导myCAF内EGFR/ERBB2信号活化, 并经AREG自分泌维持促转移状态, 提示TGF-β与RTK信号之间存在协同放大作用[42].

2.2 ECM重塑与力学传导

ECM重塑是CAF驱动EMT与转移的另一条核心主线, CAF作为构成ECM蛋白(包括胶原蛋白、纤连蛋白和层粘连蛋白等)的主要细胞来源, 可通过调控ECM的沉积、排列、交联与受体结合方式, 持续改变肿瘤细胞所处的物理和信号环境[43,44].

2.2.1 ECM成分与空间结构重塑

CAF首先通过改变ECM的组成和空间构型, 为肿瘤细胞侵袭提供结构基础. 基于单细胞与空间转录组整合分析鉴定出的ECM-remodeling CAF及其分泌的POSTN, 后者可经POSTN-ITGAV/ITGB5轴增强肿瘤细胞迁移、侵袭并与不良预后相关[45]. CAF来源FN1可通过整合素-PI3K/AKT信号促进PDAC转移表型[46]. 这些研究提示, POSTN, FN1等传统上被视为"结构成分"的基质蛋白, 实际上也是主动的信号配体, 可同时参与力学重塑、EMT维持和转移生态位构建. 与此同时, 胶原蛋白作为ECM的核心组成成分, 在肿瘤发生与进展中发挥着重要作用[47,48]. 在乳腺癌中, 上调的Ⅻ型胶原可介导Ⅰ型胶原的空间排列结构, 从而影响肿瘤细胞的侵袭[49]. 在CAF中具有高活性的黏着斑激酶(FAK)则调控了Ⅰ型和Ⅲ型胶原纤维的产生与成熟[50]. 除胶原蛋白外, 纤连蛋白也可增强CAF与肿瘤细胞之间的黏附, 并驱动肿瘤细胞定向迁移[51], 骨桥蛋白等基质分子亦参与促进肿瘤生长和侵袭[52]. 由此可见, CAF通过重塑ECM的种类、丰度及排列方式, 首先为后续的机械感知和EMT激活建立了促侵袭的基质背景.

2.2.2 ECM-细胞受体耦联与黏附信号激活

在ECM成分和结构发生改变后, 肿瘤细胞需通过特定受体将这些外部变化转译为胞内信号, 其中整合素是这一过程的关键枢纽. 作为跨膜受体, 整合素不仅介导细胞与ECM之间的黏附, 还可将外界的机械和化学刺激连接至肌动蛋白骨架及下游信号网络, 进而激活FAK/SFK, Fyn/YES, Rac/Cdc42等通路, 诱导EMT并促进细胞迁移[53]. 不同ECM分子可通过各自对应的整合素轴放大这一过程, 进而影响肿瘤进展与转移. Lumican可与整合素β1结合并激活FAK信号, 从而促进胃癌进展[54]; VCAM-1可通过整合素α4β1激活AKT和MAPK通路, 促进肺癌细胞增殖和迁移[55]; periostin可通过结合整合素αvβ3激活PI3K/AKT通路并诱导EMT, 促进卵巢癌迁移与侵袭[56]; Thrombospondin 4 (凝血酶敏感蛋白4)可通过整合素α2/HSF1轴促进胆囊癌恶性进展[57]. 在胰腺癌中, 由CAF生成的肿瘤间质TGF-β1-THBS2复合体可通过整合素αvβ3促进恶性进展[58]. 由此, ECM重塑并非停留于基质外层, 而是通过整合素介导的受体耦联, 进一步被转化为持续的促瘤信号输入.

2.2.3 组织硬度升高与机械感知启动

持续的ECM沉积、重塑和交联可导致肿瘤微环境硬度增加, 进而通过机械传导支持EMT、侵袭和转移, 并推动肿瘤恶性进展[59]. YAP/TAZ作为重要的结构和机械力学感受器, 在纤维化与肿瘤发展中发挥着重要的调控作用[60]. *RASSF1*基因的沉默会导致YAP1蓄积和P4HA2表达增高, 从而促进胶原沉积、增加ECM硬度, 并最终促进肿瘤转移[61]. 基质硬度升高可驱动YAP入核, 进而促进癌细胞增殖、分化、侵袭和转移[62]. 此外, CXCR4可通过YAP通路传递ECM硬度信号, 从而调控肝细胞癌中的细胞增殖、EMT及干细胞特性[63]. 近年来, 关于"基质力学本身即可作为EMT起始信号"的认识进一步得到强化. 已有研究表明, 单

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纯的基质硬度升高即可作为独立诱因触发上皮间质转化并促进转移[64]. 与此同时, 肿瘤-基质力学互作还能通过影响氨基酸可用性与代谢状态维持恶性生长[65], 提示ECM硬度、代谢适应与侵袭表型之间存在协同放大关系. 上述结果共同说明, 硬化的基质已不再只是被动支架, 而是持续作用于肿瘤细胞的机械刺激来源.

2.2.4 下游EMT/侵袭程序放大

在机械感知被启动之后, 基质硬度和张力信号还可进一步经多条下游通路被持续放大, 并最终输出为EMT、侵袭及转移表型. 已有研究表明, 基质硬度升高所诱发的EMT并非孤立事件, 其下游不仅涉及S100A11膜转位、eIF4E磷酸化以及TGF-β1自分泌三条与Snail表达相关的信号途径[57], 还可通过NEAT1/WNT/β-catenin通路上调ZEB1, 从而促进EMT侵袭程序[66]. 另有研究表明, 机械敏感受体EPHA2可通过募集LYN激酶磷酸化TWIST1, 从而诱导EMT[59]. SNAIL1, ZEB1与LOXL2之间存在一个正反馈环路, 可持续推动EMT进程. 除直接作用于EMT转录程序外, ECM硬度还可影响肿瘤代谢以及CAF与肿瘤细胞之间的代谢串扰, 进而促进肿瘤生长并增强侵袭性[67]. 另一方面, 整合素介导的黏附和牵引力本身亦可增强ECM重塑和组织硬化, 而这一变化又可被CAF和肿瘤细胞重新感知并进一步促进肿瘤EMT与转移[68], 形成“ECM重塑-组织硬化-机械感知-EMT激活”的循环. 例如, 整合素α3和α5是CAF进行ECM重塑所必需的, 为肿瘤侵袭提供了结构向导; 整合素α11β1在CAF中高表达, 可诱导胶原重组并增加组织硬度, 进而促进肺癌转移[69]. 因此, ECM重塑的生物学意义不仅在于提供物理支架, 更在于通过持续的力学信号输入和受体耦联, 将基质异常转化为稳定的EMT和侵袭表型.

2.3 白细胞介素

白细胞介素家族是CAF介导炎症性旁分泌的常见促EMT介质. 其中以IL-6/STAT3轴最具代表性, 可直接驱动肿瘤细胞EMT及转移. 在食管腺癌中, 主要由CAF而非肿瘤细胞分泌的IL-6可诱导EMT和肿瘤转移, 其表现为vimentin, Snail2和N-cadherin升高, 而E-cadherin和KRT19下降[70]. 在肝细胞癌中, CAF可通过IL-6/IL6R/STAT3轴诱导EMT[71]. Jia等人[72]进一步指出, CAF还可通过转谷氨酰胺酶2依赖的IL-6/IL6R/STAT3轴诱导肝细胞癌EMT, 说明IL-6相关信号不仅参与耐药, 也直接驱动侵袭性表型形成. 除IL-6外, 其他白细胞介素也参与CAF驱动的侵袭程序. 如CAF分泌的IL-1β也被证实参与肿瘤EMT和播散过程, 其可在乳腺癌[73]、口腔鳞癌[74]和头颈部肿瘤[74]中上调细胞黏附分子表达, 促进炎症-侵袭相关表型形成. 与此同时, IL-33也参与CAF与肿瘤细胞之间的正反馈放大. Lin等人[75]发现, CAF诱导的IL-33增强了头颈癌细胞自我产生IL-33的自分泌过程, 并通过SDF1/CXCR4信号通路提高了肿瘤的侵袭性. CAF分泌的IL-33还能促进肿瘤基质介导的转移, 而在小鼠体内阻断IL-33可显著减少肿瘤转移[76]. 此外, IL-32也可作为CAF促EMT效应的补充分子. 有研究指出, IL-32在CAF中丰度较高, CAF分泌的IL-32可通过整合素β3-p38 MAPK信号介导CAF与乳腺癌细胞的相互作用, 从而促进CAF诱导的乳腺肿瘤EMT和侵袭[67]. 总体而言, 白细胞介素相关信号并非孤立存在, 而是共同构成CAF驱动EMT的炎症性旁分泌网络.

2.4 CXCLs

CXCL是一类CXC趋化因子, 参与炎症细胞募集、组织损伤应答及肿瘤微环境中的细胞通讯[68]. CXCLs及其受体是炎症细胞、肿瘤细胞与CAF之间相互作用的重要分子基础, 可共同增强肿瘤转移[69]. 研究发现, 在PDAC肿瘤-基质相互作用中, CXCL配体与CXCR2阳性细胞之间的信号可促进CAF迁移及PDAC细胞侵袭; 阻断CXCLs-CXCR2轴可降低肿瘤转移率并延长小鼠生存期[69,77]. 在此基础上, 不同CXCL分子可通过不同方式放大CAF的促转移作用. 巨噬细胞来源的CXCL3激活了仅在CAF中特异表达的CXCR2, 诱导CAF向肌成纤维细胞样CAF(myCAF)转变, 从而促进了由myCAF介导的胰腺癌转移[78]. 此外, CAF衍生的CXCL11通过circUBAP2/miR-4756/IFIT1/3信号轴增强了肝细胞癌细胞的迁移及肿瘤远处转移[79].

2.5 细胞外囊泡/非编码RNA介导的远程传递

在CAF-肿瘤细胞通讯中, EVs可携带miRNA, lncRNA, circRNA及蛋白质等多类货物, 从而在局部或远程层面改变肿瘤细胞的EMT、干性和耐药表型. 需要说明的是, 非编码RNA并非都具有相同的转录、加工和稳定性特征. 例如, 部分lncRNA并不一定具有

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poly(A)尾或经历典型剪接过程. 而非编码RNA中的微小RNA(microRNA, miRNA)是一类在转录后水平调节靶标基因表达的短链核苷酸转录本[80]. CAF分泌的外泌体可将miRNA传递至肿瘤细胞, 在肿瘤转移中发挥重要作用. 多项研究表明, 外泌体来源miRNA可在多种肿瘤中通过Wnt/β-catenin通路影响EMT和转移[81,82]. CAF来源的外泌体miR-18b可特异性结合靶点TCEAL7, 并通过NF-κB通路增强Snail在核内的异位激活, 诱发EMT并促进乳腺癌细胞的侵袭与转移[83]. 另有研究显示, miR-181d-5p可通过调控CDX2/HOXA5促进乳腺癌EMT、侵袭与迁移[84]; 在非小细胞肺癌中, miR-224能提高细胞内HIF-1α的水平, 进而激活转移相关下游基因的表达. 需要指出的是, miRNA在CAF-肿瘤通讯中并非始终表现为促转移因子. 相反, 部分miRNA具有抑制EMT和转移的作用, 其在CAF外泌体中的下调或缺失, 本身也可解除对侵袭程序的抑制[85,86]. 由此可见, CAF相关非编码RNA网络的本质并不是单向“激活”, 而是对EMT调控平衡的整体重塑.

2.6 其他因子

除上述分子外, 还有一些细胞因子、趋化因子和蛋白酶效应分子同样能够诱导EMT并促进转移. SDF-1是其中较为典型的代表, CAF来源的SDF-1可在肺腺癌中通过CXCR4/β-catenin/PPARδ信号通路激活EMT[77]. 与此同时, 肝细胞癌细胞分泌的SULF2可诱导CAF分化, 而CAF来源SDF-1进一步介导SNAIL1表达并促进EMT[87]. 另有研究证实, CAF分泌PDGFC可通过激活PDGFC-PDGFRA信号上调SLUG表达; 此外, CAF产生的CCL5可抑制HIF-1α泛素化, 上调ZEB1表达, 并最终诱导EMT[79]. 除可溶性因子外, CAF相关蛋白酶效应分子也参与转移程序放大. 肿瘤细胞来源TGF-β1可经pSMAD2/3诱导CAF高表达MMP11, 后者进一步通过PI3K/AKT相关信号促进PDAC细胞EMT、侵袭与肿瘤进展, 提示CAF来源基质金属蛋白酶不仅参与ECM重塑, 也可直接驱动转移程序[88]. 值得注意的是, 炎症相关CAF程序还可通过特定钙结合蛋白和转分化信号进一步放大转移表型. CALB2可驱动胰腺癌微环境的炎症性重编程, 并通过增强肿瘤-基质互作促进远处转移, 提示炎症型CAF并非单纯伴随性改变, 而是可能直接参与转移生态位的构建[89].

2.7 CAF诱导EMT与肿瘤干细胞特性的耦联

EMT与肿瘤干细胞样特性(cancer stem cell-like properties, CSC-like properties)之间存在高度重叠的调控基础. SNAIL, ZEB和TWIST等EMT转录因子不仅降低上皮黏附并增强迁移侵袭, 也可与CD44, ALDH, SOX2, NANOG和OCT4等干性相关程序形成协同. CAF通过旁分泌TGF-β, IL-6, OPN/SPP1, Nodal/Activin及ECM力学信号, 可同时推动PDAC细胞间质化和干性维持. 例如, CAF条件培养基中的OPN/SPP1可经CD44轴增强胰腺癌细胞球形成和干性特征[90]; Nodal/Activin信号则可维持胰腺癌干细胞的自我更新和致瘤性[91]. 基质硬度升高还可经YAP/TAZ等机械转导节点将ECM异常转化为干性和耐药信号输入[63]. 由此, CAF诱导的EMT并非单纯的迁移表型改变, 而是常与“EMT-CSC-耐药-复发”连续状态耦联, 这也是单一通路抑制难以充分逆转PDAC恶性进展的重要原因.

3 CAF与肿瘤化疗耐药

肿瘤微环境(tumor microenvironment, TME)是由ECM等大分子网络及多种细胞成分共同构成的复杂生态系统, 其中包含CAFs、血管平滑肌细胞、周细胞、内皮细胞、间充质干细胞以及各类免疫细胞. 定植于间质中的CAFs是TME中最基础也是最核心的细胞成分, 其细胞来源、表型及功能均具有显著差异[92]. 活化的CAF可通过多条途径促进肿瘤生长、血管生成、侵袭与转移, 并通过推动ECM重塑等机制进一步诱导肿瘤多药耐药性[93]. 传统观点认为, CAF主要通过两种方式促进肿瘤细胞耐药: 其一为可溶性和分泌性因子介导的耐药(soluble and secretory factor-mediated drug resistance, SFM-DR), 其二为细胞黏附介导的耐药(cell adhesion-mediated drug resistance, CAM-DR). 近年来, 随着代谢重编程、免疫调控及治疗诱导基质重塑研究的推进, CAF驱动耐药的机制框架又进一步扩展为多维度耦联的系统过程, 详情见图2.

3.1 SFM-DR

SFM-DR是目前研究最为广泛的耐药模式. 该模式指CAF通过分泌各类细胞因子(包括趋化因子、生长因子及外泌体等)与其他间质细胞及肿瘤细胞进行

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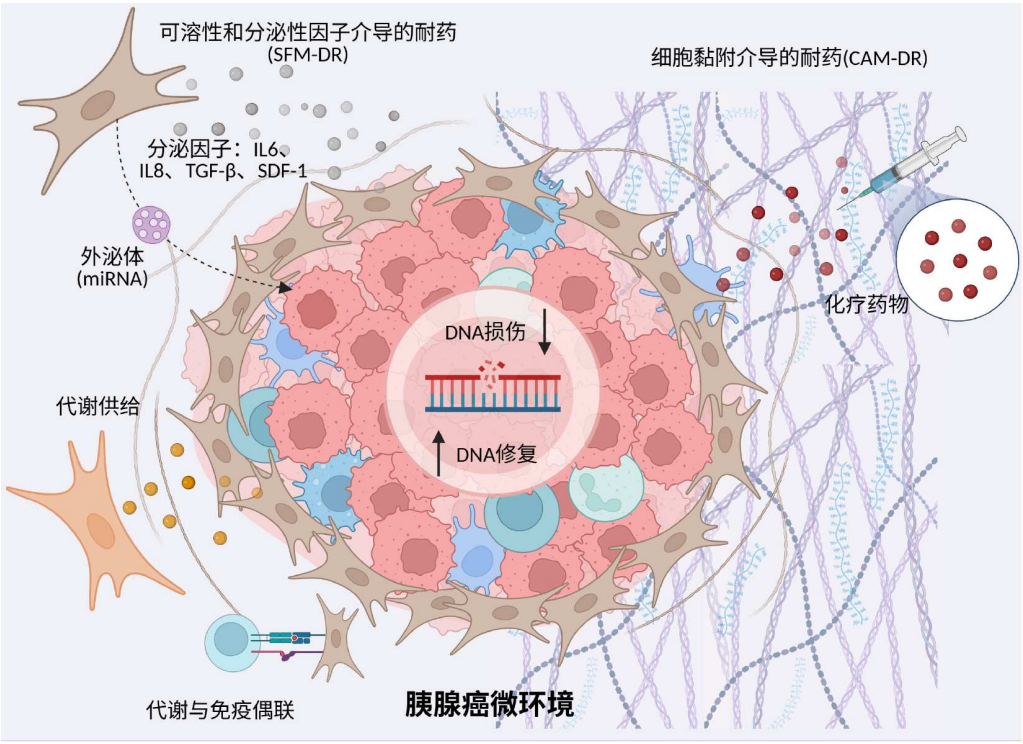


图 2 CAF通过可溶性因子、细胞黏附及代谢-免疫耦联促进肿瘤细胞化疗耐药. CAF介导化疗耐药主要通过三条相互耦联的途径实现. (ⅰ) 可溶性和分泌性因子介导的耐药: CAF分泌IL-6, IL-8, TGF-β, SDF-1及含miRNA的外泌体, 激活JAK/STAT3, PI3K/AKT等存活与抗凋亡信号; (ⅱ) 细胞黏附介导的耐药: 透明质酸与胶原等ECM成分形成高间质液压与致密物理屏障, 阻碍药物渗透, 并经整合素-FAK信号增强肿瘤细胞存活; (ⅲ) 代谢与免疫耦联: CAF通过乙酸/脂质代谢供给、外泌体货物转运及免疫调控进一步强化耐药. 三条途径共同构成系统性治疗耐受. 图件版权说明: Created in BioRender.com. Hu, Y. (2026) https://BioRender.com/vkalytx

Figure 2 CAFs promote chemoresistance of tumor cells through soluble factors, cell adhesion and metabolic-immune coupling. CAF-mediated chemoresistance is achieved mainly through three interconnected routes. (i) SFM-DR: CAFs secrete IL-6, IL-8, TGF-β, SDF-1 and miRNA-containing exosomes that activate survival and anti-apoptotic signaling such as JAK/STAT3 and PI3K/AKT; (ii) CAM-DR: hyaluronan- and collagen-rich ECM components generate high interstitial fluid pressure and a dense physical barrier that impairs drug penetration, while integrin-FAK signaling enhances tumor cell survival; (iii) metabolic and immune coupling: CAFs further reinforce resistance through acetate/lipid metabolic supply, exosomal cargo transfer and immune modulation. Together these routes constitute systemic therapeutic tolerance. Created in BioRender.com. Hu, Y. (2026) https://BioRender.com/vkalytx

频繁的信息交换, 从而促进肿瘤进展及耐药形成. 在这一过程中, 白细胞介素作为一类关键的细胞因子, 在免疫网络调节和内环境稳态维持中起着核心作用, 其中IL-6尤为关键. IL-6不仅能驱动成纤维细胞自身的活化, 还介导了肿瘤细胞与CAF间的双向通讯[94]. CAF分泌的IL-6能够激活JAK1/STAT3信号, 从而增强肿瘤化疗耐药[95,96]; 另一旁路途径则可通过上调趋化因子受体CXCR7的表达发挥作用[97]. 此外, 在小鼠PDAC模型中, 当α-SMA$^+$ CAF中的IL-6被敲除后, 吉西他滨对模型小鼠的治疗效果显著改善[98]. 除IL-6外, CAF还可分泌IL-8和IL-11以诱导肿瘤细胞耐药. 研究表明, 来源于铂类耐药PDAC患者的CAF分泌IL-8的水平高于来源于铂类敏感患者的CAF, 且CAF分泌的IL-8可通过lncRNA UPK1A-AS1介导的DNA双链断裂(double-strand break, DSB)修复促进PDAC对奥沙利铂耐药[99]. 在胃癌中, CAF分泌IL-8和IL-11同样可促进化疗耐药: 其中IL-8通过激活PI3K/AKT通路诱导奥沙利铂耐药[100], IL-11则通过激活IL-11/IL-11R/gp130/JAK/STAT3抗凋亡信号通路促进耐药[101]. 除白细胞介素网络外, TGF-β和SDF-1同样是CAF介导耐药的重要分泌因子. 在PDAC中, TGF-β常通过激活CAF来增强肿瘤细胞化疗耐药. 近期研究显示, 间质中的CAF可被TGF-β1经SMAD2/3通路激活, 并上调ATF4-ABCC1信号轴, 进而促进胰腺癌进展及吉西他滨耐药[102]; 此外,

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TGF-β1还可诱导基质来源因子CYR61下调核苷转运体hENT1和hCNT3, 从而增强胰腺癌对吉西他滨的耐药[103]. SDF-1也是介导耐药的关键分子. CAF中由VEGF/NRP2信号驱动的SDF-1分泌以及癌细胞中Hippo通路的激活, 可共同导致肿瘤细胞耐药[104]. 此外, CAF还可通过分泌外泌体促进肿瘤细胞耐药[105]. 位于肿瘤微环境中的CAF能够释放大量含有miRNA的外泌体, 并作用于肿瘤细胞, 促进肿瘤生长和耐药. 在胰腺癌及非小细胞肺癌中, CAF释放的外泌体含有靶向PTEN的miRNA(如miR-20A, miR-21, miR-181a, miR-221, miR-222和miR-92a), 可抑制PTEN并激活PI3K/AKT通路, 促进肿瘤细胞增殖与耐药[106]. CAF分泌外泌体中的miR-4717-5p还可通过抑制嘧啶类药物转运体并调节平衡型核苷转运体2(equilibrative nucleoside transporter 2, ENT2), 诱导肿瘤对抗嘧啶药物产生耐药[107]. 近年来, 越来越多的证据表明, CAF分泌的外泌体miRNA如miR-93, miR-423, miR-196a和miR-15a-5p等, 均可参与促进肿瘤细胞耐药[11,108,109]. 总体而言, SFM-DR的核心并不在于某一种单独分子, 而在于CAF通过细胞因子、生长因子及外泌体货物的持续输出, 重塑肿瘤细胞的存活、修复、药物转运及抗凋亡程序, 从而形成稳定的化疗耐受状态.

3.2 CAM-DR

除SFM-DR外, CAM-DR是导致耐药的另一重要机制. 与前者主要依赖可溶性信号不同, CAM-DR更强调CAF和ECM与肿瘤细胞之间的物理接触、黏附耦联以及由此触发的屏障效应和胞内存活信号. 早期研究已发现, 胰腺癌作为典型促结缔组织增生型肿瘤, 富含透明质酸(hyaluronan, HA)、胶原和纤连蛋白等基质成分, 可形成高间质液压(interstitial fluid pressure, IFP)和固体应力(solid stress), 从而共同限制血管灌注和药物渗透[110,111]. 尤其是高分子量HA可吸水形成凝胶样流体相, 并使PDAC组织压力升高至远高于正常组织的水平; PEGPH20降解HA可在模型中降低压力并改善递送[111]. 与此同时, HA和胶原等ECM成分还可通过固体应力压迫肿瘤血管, 使有效灌注面积下降并进一步造成化疗药物进入不足[112]. 临床转化层面, PEGPH20联合白蛋白紫杉醇/吉西他滨虽在早期研究中显示改善基质屏障的潜力[113], 但HALO 109-301 Ⅲ期研究未能改善HA-high转移性PDAC患者总生存, 提示单纯“物理疏通”基质并不足以稳定转化为生存获益, 仍需与亚群分层、免疫调节或代谢干预联合. 随后研究发现, TME中的CAF可通过分泌胶原和纤连蛋白促进肿瘤“愈合样”基质形成, 致密基质包绕癌细胞, 导致化疗药物难以渗透进入肿瘤内部, 并限制抗肿瘤药物与癌细胞的有效接触, 最终引发胰腺癌耐药[110,114]. 在此基础上, 肿瘤细胞与ECM之间的黏附又可进一步转化为促耐药的胞内信号. 整合素是介导肿瘤细胞与ECM相互作用的重要黏附受体; 当肿瘤细胞黏附于ECM或基质细胞后, 可通过p21/p27相关细胞周期停滞、FAK/PI3K/AKT存活信号及药物外排通路增强耐受. 近期研究还提示, CAF与肿瘤细胞可通过连接蛋白介导的细胞间通讯转移Zn^{2+}并调控ABCB1等外排相关程序[115]. 因此, CAM-DR并非单纯“黏住后不敏感”, 而是由高压屏障、血管压迫、药物扩散不足和黏附诱导存活信号共同构成的复合耐药模式. 总体而言, CAF既可通过促进致密基质形成而间接诱导耐药, 也可通过其分泌因子或直接细胞接触激活肿瘤细胞内信号通路而直接增强耐药. 因此, 靶向CAF被视为逆转肿瘤耐药的重要策略之一.

3.3 代谢与免疫耦联介导的耐药新进展

除上述两类经典机制外, 近年来的研究表明, CAF介导耐药并非仅仅表现为“分泌因子作用”或“物理屏障阻挡”, 而是逐渐呈现出代谢重编程、免疫调控、力学重塑与治疗诱导状态转换相互耦联的特征. 代谢互作已成为理解CAF介导耐药的重要切入点. Murthy等人[116]报道, CAF来源乙酸可通过肿瘤细胞ACSS2-SP1-SAT1轴改变多胺代谢, 增强其在酸性微环境中的生存优势与治疗耐受; *SETD2*缺失的胰腺癌细胞可塑造ABCA8a^{+}脂质富集型CAF, 该类CAF向癌细胞输出脂质以维持线粒体氧化磷酸化, 提示CAF可通过营养供给和代谢重编程赋予肿瘤更强的适应性和耐药表型[117]. 其次, 基质成分、炎症因子与代谢信号之间也存在紧密联动. 除乙酸和脂质供给外, 胰腺星状细胞与肿瘤细胞之间围绕透明质酸和IL-6形成的双向串扰, 同样能够强化耐药形成. 胰腺星状细胞通过透明质酸和IL-6相关旁分泌信号可促进胰腺癌进展及化疗耐受, 提示基质成分、炎症因子与治疗反应之间存在更紧密的联动关系[118]. 治疗诱导的基质重塑亦是耐药形成过程中不可忽视的维度. 获得耐药的PDAC细胞与基质

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成纤维细胞之间的黏附与力学互作发生系统性改变, 提示耐药并非单纯的肿瘤细胞内事件, 而伴随可测量的细胞-基质生物力学重编程[119]; 在旁分泌共培养体系中, PSC的转录组会随其与癌细胞空间距离变化而呈现梯度改变, 说明可溶性因子介导耐药与细胞黏附介导耐药在真实肿瘤中更接近连续谱, 而非彼此孤立的两类机制[120]. 进一步地, 脂质代谢与外泌体货物转运也被纳入CAF介导耐药的机制框架. 脂质负荷型成纤维细胞可通过外泌体转移PKM2增强肿瘤细胞化疗耐受, 提示CAF介导的耐药不仅涉及营养底物供给, 还涉及代谢酶及EV货物的定向输出[121]. 由此可见, 脂质代谢、乙酸代谢与外泌体信号传递可能共同构成PDAC中CAF驱动耐药的关键代谢轴. 与此同时, CAF介导的耐药还深受炎症和免疫调控网络影响. CAF维持的FGF1信号可削弱RAF-MEK抑制所致的MYC下调, 导致RAS/MAPK抑制耐受, 而FAK抑制联合RAF-MEK抑制可重编程基质并恢复对细胞毒及免疫治疗的敏感性[122]. 阻断CAF表面IL1RAP可抑制IL-1驱动的趋化因子分泌及中性粒细胞/单核细胞募集[123]; LIFR竞争性抑制剂EC359可增强吉西他滨/白蛋白紫杉醇疗效[124]. 胰腺酶原可重塑PDAC相关成纤维细胞的分泌谱和活化状态[125]; CAF来源外泌体可通过NOD1通路调控巨噬细胞极化, 从先天免疫层面进一步强化促瘤微环境[126]. 与此相应, TGF-β阻断可促进PDAC恶性细胞向经典型状态偏移并增强联合化疗敏感性[127]. 总体而言, CAF介导耐药的机制已由早期强调“药物渗透不足”或“单一旁分泌因子作用”的框架, 扩展为炎症、代谢、外泌体、基质重塑及免疫调控共同维持的系统性治疗耐受. 这一认识也提示, 未来逆转PDAC耐药的策略, 可能更依赖于对CAF-肿瘤细胞-免疫/代谢网络的联合干预, 而非针对单一通路的局部阻断.

4 CAF靶向治疗策略

CAF通过分泌细胞因子、趋化因子以及与肿瘤细胞的直接接触, 在肿瘤起始、进展和药物耐受中发挥极其重要的作用, 而CAF与肿瘤细胞之间的相互作用又受到复杂而精细的信号网络调控[11]. 靶向治疗是指直接针对参与肿瘤发生、肿瘤生长和耐药形成的关键分子实施干预的治疗模式, 可作为化疗、放疗和免疫治疗的重要辅助手段. 因此, CAF在肿瘤发展过程中所表现出的特异性特征, 包括异常激活的信号通路及相关分子改变, 均为肿瘤治疗提供了潜在而有前景的靶点[128]. 根据治疗机制不同, CAF靶向治疗策略主要可分为三类: CAF清除、CAF功能抑制以及CAF正常化, 目前靶向CAF治疗策略相关研究进展详情见表2.

表 2 CAF相关代表性干预策略/临床研究及转化启示[a)]

Table 2 Representative CAF-related intervention strategies/clinical studies and translational implications[a)]

策略/药物	靶点/机制	研究阶段或试验	适应症/背景	主要结果或启示
Galunisertib+吉西他滨	TGF-βRI(ALK5)抑制	Phase Ⅱ	不可切除胰腺癌	联合方案较吉西他滨单药显示总生存获益信号, 安全性可接受[129]
Galunisertib+Durvalumab	TGF-βRI+PD-L1	NCT02734160, Phase Ib	转移性胰腺癌	耐受性可接受, 但临床活性有限, 提示需更精确分层[130]
Tocilizumab+Gem/nab-PTX	IL-6R阻断	NCT02767557, 随机Phase Ⅱ	晚期胰腺癌一线	未达到6个月OS主要终点, 但18个月OS和抗恶病质方面出现信号[95,131,132]
Tocilizumab+Gem/nab-PTX再挑战	IL-6R阻断	日本Phase Ⅰ	Gem/nab-PTX进展后转移性胰腺癌	小样本中出现肿瘤缩小, 支持继续探索CAF/炎症抑制联合化疗[113,133]
PEGPH20/pegvorhyaluronidase alfa	HA降解、降低IFP和固体应力	HALO 109-301, Phase Ⅲ	HA-high转移性PDAC	未改善总生存, 提示单纯基质去除需结合分层和联合治疗[113]
FAP靶向策略	FAP疫苗、BiTE、CAR巨噬细胞、FAPI成像/放射配体	临床前至早期临床	CAF-rich实体瘤/PDAC	可实现CAF定位或免疫杀伤, 但需避免非选择性破坏保护性基质[134~136]
VDR激活/Calcipotriol	PSC/CAF正常化	临床前及组合探索	PDAC基质重编程	可促进星状细胞静息化并增强吉西他滨递送, 但免疫效应需谨慎评估[137,138]

a) Gem/nab-PTX: gemcitabine plus nab-paclitaxel; FAP: fibroblast activation protein; VDR: vitamin D receptor

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4.1 CAF清除

针对CAF表面特异性分子标志物的直接物理清除或削弱策略，已在多种实验模型中显示出一定抗肿瘤潜力. 经典CAF标志物α-SMA和成纤维细胞活化蛋白(fibroblast activation protein, FAP)已被广泛应用于CAF靶向治疗研究[134]. 然而, 选择性去除α-SMA$^+$肌成纤维细胞不仅未能遏制肿瘤，反而因破坏了基质的某些抑癌屏障功能诱发了更深度的全身免疫抑制，并促进胰腺癌进展[139]. 相比之下，靶向FAP的治疗在多项研究中显示出较大潜力[135,140,141]. 一方面, FAP靶向疫苗可增加肿瘤组织中CD8$^+$和CD4$^+$ T细胞浸润, 从而增强抗肿瘤免疫反应[136,142]. 新近开发的肿瘤疫苗eNVs-FAP不仅能够重塑肿瘤微环境以促进抗肿瘤免疫，还可通过干扰素-γ诱导肿瘤铁死亡，形成双重抗肿瘤效应[143]. 另一方面，以溶瘤腺病毒驱动的免疫治疗可诱导特异性免疫攻击，从而清除CAF[144]; 针对FAP靶点的双特异性T细胞接合器(BiTE)病毒重组体，能像“分子桥梁”一样强效交联并激活细胞毒性T细胞从而增强抗肿瘤效应[145~147]. 在此基础上, 融合了光学物理学与免疫学的新兴FAP靶向光免疫疗法(photoimmunotherapy), 因具有较高的时空精准性并可能降低全身毒性，正在成为值得关注的CAF靶向方向[148]. 除直接针对FAP阳性成纤维细胞外，基于溶瘤病毒的平台也提示，靶向肿瘤相关周细胞或其他FAP相关基质细胞同样可能重塑肿瘤微环境. 有研究在胶质母细胞瘤模型中证实，溶瘤病毒可识别并攻击FAP表达的肿瘤相关周细胞，从而增强肿瘤微环境干预效果. 这一结果虽然来源于非胰腺癌模型，但从策略层面为胰腺癌基质清除提供了可借鉴思路[144]. 在CAF清除策略方面, FAP靶向已由传统抗体或细胞治疗进一步延展至体内可递送的CAR巨噬细胞体系. 新近构建的体内FAP-CAR巨噬细胞可在原位PDAC模型中降低FAP表达、胶原沉积与Col1a1分泌，增强吉西他滨递送及免疫细胞浸润，从而提升化疗和免疫治疗敏感性并延长生存, 提示“去纤维化+增强药物进入”的双重获益可能是FAP靶向的重要优势[149].

4.2 CAF功能抑制

在多种肿瘤背景下，CAF内部多条信号通路可呈持续激活状态，从而促进肿瘤细胞增殖、转移、侵袭及耐药. 因此，靶向CAF特定信号通路以抑制其促肿瘤功能、增强抗肿瘤治疗效果，是一种可行的策略. 当前，针对IL-6及其受体和下游信号分子的干预研究已较为深入[131,132]. 抗IL-6R单克隆抗体托珠单抗(tocilizumab)可抑制IL-6/JAK1/STAT3经典致炎与存活信号传导, 从而在多个实验模型中增强化疗药物效力[95]. Tranilast同样可抑制IL-6分泌, 发挥类似作用[150]. 此外, IL-6抗体与PD-L1抗体的联合治疗可在胰腺癌中抑制肿瘤发展[151]. 除IL-6通路外，其他关键分子和信号轴也被用于CAF靶向治疗研究. CAF对SLC7A11具有高度依赖性, 靶向*SLC7A11*基因可降低CAF活性, 从而抑制肿瘤生长[152]. 另有研究显示, CAF分泌的PDGFC可促进胃肠间质瘤生长和转移, 提示PDGFC-PDGFRA相关轴也可能具有干预价值[153]. 在CAF功能抑制层面, LIF/LIFR信号正逐渐显现为具有转化潜力的新靶点. Bhatia等人[124]报道，LIFR竞争性抑制剂EC359在含CAF共植的胰腺癌模型中可显著降低肿瘤负荷，并在自发性PDAC模型中增强吉西他滨/白蛋白紫杉醇疗效, 同时伴随树突状细胞增多和调节性T细胞减少. 这一结果提示，抑制CAF分泌依赖的促瘤细胞因子网络, 有望同步改善药物敏感性与免疫微环境.

4.3 CAF正常化与重编程

除直接清除CAF外，通过抑制CAF活化并使其恢复至相对静息状态，从而减少活化CAF数量，也是重要的治疗策略. 鉴于TGF-β过度表达可诱导CAF形成, 因此已有多种靶向TGF-β的药物进入临床研究阶段, 如galunisertib，fresolimumab，trabedersen和vactosertib[129]. 其中，作为TGF-β受体Ⅰ激酶抑制剂的galunisertib，在与抗PD-L1抗体durvalumab联用[130]以及与新辅助放化疗联合应用[154]方面均显示出一定研究价值. 此外，HSP90抑制剂XL888可抑制PSC和CAF活化，从而提高PDAC中PD-1阻断治疗的效果[155]. 维生素D受体(vitamin D receptor, VDR)能够促使PSC和CAF恢复静息状态，进而促进基质重塑并增强吉西他滨的化疗效力[137]. 基于这一机制，VDR激活联合自噬阻断策略可进一步增强星状细胞重编程效果，并改善PDAC免疫治疗反应[156]. 从机制层面看，TGF-β信号通路仍是CAF正常化与纤维化逆转策略的核心靶点之一. 针对TGF-β信号转导的干预不仅具有抗纤维化潜力，也可能通过重塑基质生态而改善抗肿瘤治疗反应[129]. 因

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此, 在PDAC这类高度纤维化肿瘤中, TGF-β靶向治疗的价值不仅体现在抑制肿瘤细胞本身, 更体现在其对CAF状态和间质屏障的整体重塑. 需要注意的是, 维生素D受体激活虽被视为促使CAF恢复相对静息状态的重要途径, 但其免疫学后果并非单向有利. calcipotriol可促使人胰腺CAF呈现更偏向抗肿瘤的表型, 但同时可能削弱T细胞介导的免疫反应[138]. 这提示CAF正常化策略在临床转化中仍需在“抑制纤维化”和“维持有效抗肿瘤免疫”之间取得更精细的平衡. CAF正常化/重编程正在成为比单纯“去除CAF”更具选择性的干预思路. 采用BET抑制剂JQ1干预活化PSC的超级增强子程序, 可减弱纤维化反应、改善血管化并促进药物递送, 从而提高化疗和免疫治疗效果[157]. STING激动剂可诱导FAP^+细胞向具有肿瘤限制作用的ifCAF样状态转化, 为“将促肿瘤CAF重新教育为抑瘤CAF”提供了概念验证. 由此可见, 未来CAF干预未必局限于“去除”, 更可能走向“选择性重塑与功能矫正”[18].

4.4 精准分层与联合干预前景

随着单细胞测序、空间组学及功能筛选技术的快速发展, CAF靶向策略正在由早期相对粗放的“泛去除”思路, 逐步转向以亚群识别和状态调控为核心的精准干预模式. 既有研究表明, 不同PDAC分子亚型与特定CAF状态之间存在较为稳定的耦联关系[15,16], 而SenCAF, ifCAF及$PLXDC1^+$肿瘤相关胰腺星状细胞等亚群在免疫抑制、纤维化维持、肿瘤限制或治疗反应中的作用并不一致[17~19]. 因此, 较为合理的治疗构想并非无差别清除全部CAF, 而是在患者分层基础上, 将FAP靶向清除、LIF/LIFR抑制、STING诱导CAF重编程以及化疗或免疫治疗联合应用, 以期提高疗效并尽可能减少对潜在保护性CAF亚群的非选择性损伤. 这一趋势也与近年的研究方向形成呼应. CAF靶向治疗正在从“去除单一细胞群”逐步转向“利用CAF可塑性并重塑其功能状态”[158]; 相关综述则从更广义的角度总结了CAF在肿瘤进展与治疗耐受中的双重作用, 进一步支持将CAF视为动态干预对象而非静态背景成分[159]. 这一认识也意味着, CAF研究正在由以标志物命名亚群的描述性阶段, 逐步过渡到结合空间位置、功能状态、治疗背景和时间窗口的综合分层框架[160~163]. 换言之, 真正具有转化意义的问题, 已不再只是“哪些CAF具有促瘤作用”, 而是“何类CAF在何种空间生态位、何种治疗背景及何种疾病阶段下发挥何种生物学效应”. 只有在这一层面上建立更具解释力的分层体系, CAF靶向治疗才可能摆脱经验性尝试, 进入可预测、可验证和可优化的阶段. 与此同时, *STK11*缺失CAF所揭示的CAF-CAF串扰增强及抗原呈递缺陷[22]提示, 未来的干预视角也不应局限于CAF与肿瘤细胞之间的双向互作, 还需进一步识别CAF内部网络中具有主导作用的状态节点. 对这些节点的解析, 有望为联合治疗提供更高层级的切入点, 即通过改写CAF群体内部的信号传播方式, 间接重塑肿瘤免疫生态和药物应答格局. 从方法学与转化路径来看, 患者来源3D共培养体系、类器官-CAF联合模型及可控生物材料平台, 正在成为解析CAF驱动耐药、验证机制并筛选联合干预方案的重要工具[164]. 与此同时, 对于PDAC异质性的理解也必须同步纳入基质状态、免疫构成和代谢耦联维度[165,166]; 而表观遗传可塑性的研究进一步提示, CAF与肿瘤细胞的状态转换可能共享部分调控框架[167]. 由此看来, 未来CAF研究的关键已不只是持续发现新的亚群名称, 而是将“状态转换规则”“空间生态位特征”与“可干预节点”有机对应起来, 形成真正具有预测与指导价值的分层模型.

从临床转化角度看, CAF靶向治疗的核心难点在于“靶点特异性不足、亚群功能双向性、药物进入障碍和疗效预测标志物缺乏”四个方面. 一方面, α-SMA或FAP等标志物并不能完全区分促瘤与抑瘤性CAF, 非选择性清除可能破坏限制肿瘤扩散的基质屏障; 另一方面, PEGPH20 Ⅲ期阴性结果说明, 仅通过降低HA和IFP改善药物递送并不一定足以带来生存获益. 因此, 未来CAF治疗更应强调患者分层和联合策略: 在CAF-rich或HA-high人群中探索基质屏障解除与化疗联用; 在IL-6/STAT3, LIF/LIFR或TGF-β信号活跃人群中进行功能抑制; 在存在ifCAF或可诱导干扰素应答的背景下, 尝试STING相关CAF重编程. 空间转录组和多重成像可进一步定位CAF-肿瘤-免疫生态位, 识别肿瘤边界、围神经侵犯和免疫排斥区域中的关键互作, 为后续临床试验提供更精准的入组依据[28,133].

5 总结与展望

总体而言, CAF并非单一的促瘤细胞群, 而是由不同细胞来源、分化状态、空间位置及治疗暴露历史共

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同塑造的动态细胞生态. 围绕CAF异质性、空间生态位、神经侵犯、代谢重编程及免疫调控的研究, 正在推动该领域由“CAF促进EMT和耐药”的宏观概括, 逐步走向对“何类CAF、在何处、通过何种机制、于何种阶段主导疾病演进”的精细化解析. 从研究范式上看, 未来工作需要进一步整合空间转录组、单细胞多组学、表观组学及谱系追踪等技术, 以厘清CAF亚群的起源、可塑性及治疗诱导状态转换, 尤其应关注表观遗传可塑性如何参与微环境重编程[167]. 同时, 在EMT、神经侵犯、转移定植及化疗耐药等关键生物学过程中, 研究重点也应由单纯的共定位或相关性描述, 推进到CAF亚群-肿瘤细胞状态-免疫构成之间因果链条的系统建立[23,24,168]. 患者来源类器官、3D共培养体系、生物材料模型与体内功能验证的联合应用, 则将是提升机制研究可转化性的关键路径[164]. 更进一步地看, CAF领域当前值得持续关注的前沿方向, 集中体现在三个层面: 其一, 是CAF内部网络及状态主导关系的解析, 尤其是CAF-CAF串扰如何塑造免疫抑制和治疗耐受[22,26]; 其二, 是具有肿瘤限制潜能的csCAF和ifCAF等亚群的诱导、稳定与利用[18,169]; 其三, 则是TAGLN, LIF/LIFR, IL1RAP, FGF1及代谢-外泌体轴等可干预节点的系统验证, 以及基于膜蛋白、多组学和空间信息的CAF分层体系在预后评估和治疗决策中的应用前景[25,26,122~124,170]. 对这些问题的深入整合, 不仅有助于提升CAF研究的理论深度, 也将为PDAC精准治疗提供更坚实的基质生物学依据.

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CAF enhances pancreatic cancer EMT and chemo-resistance

ZHANG ShaoBo, ZENG Qiong & LIU MingYang*

State Key Laboratory of Molecular Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100021, China
** Corresponding author, E-mail: liumy@cicams.ac.cn*

Pancreatic ductal adenocarcinoma (PDAC) is characterized by high invasiveness, a propensity for early metastasis, and poor response to multiple therapeutic modalities. Its highly fibrotic tumor microenvironment is considered an important basis for disease progression and treatment failure. Cancer-associated fibroblasts (CAFs) are critical components of the tumor microenvironment. Rather than constituting a single pro-tumor cell population, CAFs represent a dynamic ecosystem composed of inflammatory CAFs, myofibroblastic CAFs, antigen-presenting CAFs and newly defined states such as senescent CAFs, interferon-response CAFs and MAPK-high CAFs. CAFs promote epithelial-mesenchymal transition (EMT), cancer stem cell-like properties, local invasion and metastatic dissemination through several interconnected axes, including TGF-β/SMAD and non-canonical PI3K/AKT or MAPK signaling, IL-6/STAT3 inflammatory signaling, CXCL-CXCR chemokine networks, extracellular matrix-integrin-FAK/YAP mechanotransduction and extracellular vesicle/non-coding RNA-mediated communication. In parallel, CAFs shape chemoresistance by increasing interstitial pressure and drug-penetration barriers, inducing cell adhesion-mediated drug resistance, rewiring metabolic support, establishing immune exclusion and undergoing therapy-induced state transitions. These studies have driven the research on CAFs from a rough framework of viewing them as a "single pro-tumor cell population" toward a mechanistic dissection of "distinct subpopulations with specific functions and spatiotemporal intercellular interactions." This article systematically reviews the molecular mechanisms by which CAFs promote EMT and chemoresistance in pancreatic cancer, and integrates recent research progress on CAF heterogeneity and precision intervention strategies. It aims to summarize, from a mechanistic perspective, the key pathways through which CAFs drive malignant progression of PDAC, and to discuss the potential value of targeting CAF subpopulations and combination therapy in future translational research.

PDAC, cancer-associated fibroblasts, epithelial-mesenchymal transition, chemoresistance, CAF heterogeneity

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